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EXAMINER	
KUBELIK, ANNE R	
ART UNIT	PAPER NUMBER
1638	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/552,857	SPANGENBERG ET AL.	
	Examiner	Art Unit	
	Anne R. Kubelik	1638	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *65-73 and 75-82* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *65-73 and 75-82* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The finality of the Office action mailed 22 October 2010 is withdrawn in favor of the new rejections below.

2. Claims 65-73 and 75-82 are pending.

3. In the response filed 13 October 2009, Applicant elected group II (SEQ ID NOs:2 and 10 and optionally SEQ ID NO:14). The portions of the claims drawn to a nonelected invention (SEQ ID NOs:3-8, 11-12 and 15-16) are withdrawn from consideration.

4. The claims contain sequences drawn to an invention nonelected with traverse in the response filed 13 October 2009. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144). See MPEP § 821.01.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 65-73, 75-80 and 82 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The rejection is modified from the rejection set forth in the Office action

mailed 22 October 2010, as applied to claims 65-73, 75-77, 79-80 and 82. Applicant's arguments filed 20 December 2010 have been fully considered but they are not persuasive.

The essential features of the claims are constructs comprising a) a nucleic acid encoding SEQ ID NOs:2, 4, 6, or 8, a nucleic acid encoding SEQ ID NO:10, and, optionally, a nucleic acid encoding SEQ ID NOs:12, 14 or 16, b) full-length complements of those sequences or full-length sequences antisense to those sequences, c) 60 bp-long "functionally active fragments" of those nucleic acids, and d) variants that have at least 90% identity to any of these sequences, wherein the sequences modify the levels of chalcone synthase, "BANYULS" and leucoanthocyanidine reductase in a plant cell. c) and d) encompass both complements and antisense sequences and those encoding chalcone synthase, "BANYULS" and leucoanthocyanidine reductase.

Nucleic acid encoding SEQ ID NO:2, 10 and 14 are the elected sequences; these include SEQ ID NO:1, 9 and 13.

The specification does not describe the "BANYULS" function.

The closest the specification comes to describing the "BANYULS" function is the following from pg 2, lines 19-22:

> The Arabidopsis BANYULS gene encodes a dihydroflavonol 4-reductase-like protein (BAN) that may be an anthocyanine reductase (ACR). The reaction catalysed by BAN is considered to be one possible branching point from the general flavonoid pathway to the condensed tannin biosynthesis.

It is not clears from this or any other part of the specification of the "BANYULS" function is a dihydroflavonol 4-reductase or an anthocyanine reductase or even which enzymatic reaction such a protein catalyzes. In arguments filed 18 August 2010, Applicant urged that BAN was now thought to be an anthocyanine reductase; if that is the case, it is suggested that "BANYULS" be replaced with --anthocyanine reductase--.

The specification does not describe 60 bp long chalcone synthase-, *"BANYULS"*- and leucoanthocyanidine reductase-encoding nucleic acids.

The specification describes no 60 bp long chalcone synthase-, "BANYULS"- and leucoanthocyanidine reductase-encoding nucleic acids. A 60 bp long nucleic acid can only encode a protein of a 20 amino acid long maximum length, too short to encode a chalcone synthase, "BANYULS" or leucoanthocyanidine reductase. Thus, the claimed nucleic acid feature cannot have the described function.

The specification does not describe the full scope of chalcone synthase-, *"BANYULS"*- and leucoanthocyanidine reductase-encoding nucleic acids with 90% identity to SEQ ID NO:1, 9 and 13.

Nucleic acids with 90% identity to the 1447 nucleotide long SEQ ID NO:1 would have 144 nucleotide substitutions relative to the 389 amino acid long chalcone synthase-encoding SEQ ID NO:2, and thus encompass nucleic acids encoding proteins with 144 amino acid substitutions relative to SEQ ID NO:2. These proteins would have 63% identity to SEQ ID NO:2.

Similarly, nucleic acids with 90% identity to the 1309 nucleotide long SEQ ID NO:9 would have 130 nucleotide substitutions relative to 338 amino acid long "BANYULS"-encoding SEQ ID NO:10, and thus encompass nucleic acids encoding proteins with 130 amino acid substitutions relative to SEQ ID NO:10. These proteins would have 61.5% identity to SEQ ID NO:10.

Nucleic acids with 90% identity to the 1551 nucleotide long SEQ ID NO:13 would have 155 nucleotide substitutions relative to 356 amino acid long leucoanthocyanidine reductase-encoding SEQ ID NO:14, and thus encompass nucleic acids encoding proteins with 155 amino acid substitutions relative to SEQ ID NO:14. These proteins would have 56.4% identity to SEQ ID NO:14.

The specification does not describe the structural features of a "BANYULS" with 61.5% identity to SEQ ID NO:10, or a leucoanthocyanidine reductase with 56.4% identity to SEQ ID NO:14, and thus does not describe the nucleic acids encoding them.

The structural features that distinguish those nucleic acids that modify the levels of chalone synthase, dihydroflavonal 4-reductase and leucoanthocyanidine reductase in a plant cell from those that do not are not described in the specification.

Hence, Applicant has not, in fact, described the constructs the full scope of the claims, and the specification fails to provide an adequate written description of the claimed invention.

Therefore, given the lack of written description in the specification with regard to the structural and functional characteristics of the claimed compositions, Applicant does not appear to have been in possession of the claimed genus at the time this application was filed.

Response to Applicant's arguments

Applicant urges that pg 5-6 of the specification discuss conservative substitutions and provide a explanation of the sequences in an alignment of sequences provided 18 August 2010; these alignments indentify conserved regions (response pg 12-13).

This is not found persuasive. The paragraph spanning pg 5-6 defines "functionally active" fragments and variants as those that modify flavonoid biosyntheses in a plant and indicates that they can have modification and/or a certain percent identity. Conservative amino acid substitutions are provided as an example of such a modification. This paragraph in the specification does not describe the structural features of those nucleic acids that modify the levels of chalone synthase, dihydroflavonal 4-reductase and leucoanthocyanidine reductase in a plant cell; it merely defines the desired outcome, as not all fragments or variants with 90% identity or those with only conservative substitutions, will have the desired function.

See Ariad Pharmaceuticals, Inc. v. Eli Lilly & Co., 94 USPQ2d 1161 (Fed. Cir. 2010) at pg 1171:

> For example, a generic claim may define the boundaries of a vast genus of chemical compounds, and yet the question may still remain whether the specification, including original claim language, demonstrates that the applicant has invented species sufficient to support a claim to a genus. The problem is especially acute with genus claims that use functional language to define the boundaries of a claimed genus. In such a case, the functional claim may simply claim a desired result, and may do so without describing species that achieve that result. But the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus…
>
> [M]erely drawing a fence around the outer limits of purposed genus is not an adequate substitute for describing a variety of materials constituting the genus and showing that one has invented a genus and not just a species.

The other leucoanthocyanidine reductase sequences in the specification, SEQ ID NOs:12 and 16, have greater than 99% identity to SEQ ID NO:14. Thus, a comparison of these sequences does not provide guidance for making sequences encoding leucoanthocyanidine reductases with 56.4% identity to SEQ ID NO:14. The specification only described one "BANYULS" sequence.

7. Claims 65-73, 75-80 and 82 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods of increasing CHS, BAN and LAR levels in a plant by transforming with nucleic acids encoding SEQ ID NO:2, 10 and 14, methods of reducing CHS, BAN and LAR levels in a plant by transforming with nucleic acids encoding SEQ ID NO:2, 10 and 14, full-length complements of those sequences or full-length sequences antisense to those nucleic acids, 60 bp-long fragments of those nucleic acids, or nucleic acids that have at least 90% identity to any of these sequences, and plants thereby produced, does not reasonably provide enablement for methods of increasing CHS, BAN and LAR levels in a plant by transforming with chalcone synthase-, "BANYULS"- and leucoanthocyanidine reductase-encoding nucleic acids with 90% identity to SEQ ID NO:1, 9 and 13 or with chalcone synthase-, "BANYULS"- and leucoanthocyanidine reductase-encoding 60 bp fragments of nucleic acid encoding SEQ ID NO:2, 10 and 14. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are broadly drawn to constructs comprising a) a nucleic acid encoding SEQ ID NOs:2, 4, 6, or 8, a nucleic acid encoding SEQ ID NO:10, and, optionally, a nucleic acid encoding SEQ ID NOs:12, 14 or 16, b) full-length complements of those sequences or full-length sequences antisense to those sequences, c) 60 bp-long "functionally active fragments" of those nucleic acids, and d) variants that have at least 90% identity to any of these sequences, wherein the sequences modify the levels of chalcone synthase, "BANYULS" and leucoanthocyanidine reductase in a plant cell. c) and d) encompass both complements and antisense sequences and those encoding chalcone synthase, "BANYULS" and leucoanthocyanidine reductase. The

claims are also drawn to plants comprising the constructs and having modified levels of CHS and BAN and optionally LAR, methods transforming a plant with the constructs to modify tannin biosynthesis, protein binding, metal chelation, antioxidation, UV-light absorption, plant defense to a biotic stress, and forage quality of a plant by disrupting protein foam and/or conferring protection from rumen pasture bloat.

Nucleic acid encoding SEQ ID NO:2, 10 and 14 are the elected sequences; these include SEQ ID NO:1, 9 and 13.

The instant specification fails to provide guidance for how to make chalcone synthase-, *"BANYULS"*- and leucoanthocyanidine reductase-encoding nucleic acids with 90% identity to SEQ ID NO:1, 9 and 13, respectively.

As discussed above, such nucleic acids encompass those encoding a chalcone synthase with 63% identity to SEQ ID NO:2, a "BANYULS" with 61.5% identity to SEQ ID NO:10, and a leucoanthocyanidine reductase with 56.4% identity to SEQ ID NO:14, respectively.

The instant specification fails to provide guidance for which amino acids of SEQ ID NO:2, 10 and 14 can be altered and to which other amino acids, and which amino acids must not be changed, to maintain chalcone synthase, "BANYULS" and leucoanthocyanidine reductase activities of the encoded proteins. The specification also fails to provide guidance for which amino acids can be deleted and which regions of the protein can tolerate insertions and still produce a functional enzyme.

The guidance in the specification with respect to making amino acid substitutions in variants is as follows:

The paragraph spanning pg 5-6 defines "functionally active" variants as those that modify flavonoid biosyntheses in a plant and indicates that they can have modification and/or a certain percent identity. Conservative amino acid substitutions are provided as an example of such a modification.

The other leucoanthocyanidine reductase sequences in the specification, SEQ ID NOs:12 and 16, have greater than 99% identity to SEQ ID NO:14. Thus, a comparison of these sequences does not provide guidance for making sequences encoding leucoanthocyanidine reductases with 56.4% identity to SEQ ID NO:14.

The specification provides only one "BANYULS" sequence.

Thus, the specification provides little or guidance as to the critical structures of the proteins.

Further, making amino acid substitutions in proteins is unpredictable.

Making "conservative" substitutions (e.g., substituting one polar amino acid for another, or one acidic one for another) does not produce predictable results. Hill et al (1998, Biochem. Biophys. Res. Comm. 244:573-577) teach that when three histidines that are maintained in ADP-glucose pyrophosphorylase across several species are substituted with the "nonconservative" amino acid glutamine, there is little effect on enzyme activity, while the substitution of one of those histidines with the "conservative" amino acid arginine drastically reduced enzyme activity (see Table 1).

Guo et al (2004, Proc. Natl. Acad. Sci. USA 101: 9205-9210) teach that while proteins are fairly tolerant to mutations resulting in single amino acid changes, increasing the number of substitutions additively increases the probability that the protein will be inactivated (pg 9209,

right column, paragraph 2). Thus, making and analyzing proteins with up to 155 amino acid substitutions that also have the required enzymatic activities would require undue experimentation.

Thus, extensive teachings are required for making nucleic acids encoding a chalcone synthase with 63% identity to SEQ ID NO:2, a "BANYULS" with 61.5% identity to SEQ ID NO:10, and a leucoanthocyanidine reductase with 56.4% identity to SEQ ID NO:14, as encompassed by the claimed nucleic acids. These teachings are not provided for by the specification. The specification also fails to overcome the unpredictability of making large numbers of amino acid substitutions in these enzymes as it provides no working examples of proteins with up to 155 amino acid substitutions.

The specification does not teach 60 bp long chalcone synthase-, *"BANYULS"*- and leucoanthocyanidine reductase-encoding nucleic acids.

The specification teaches no 60 bp long chalcone synthase-, "BANYULS"- and leucoanthocyanidine reductase-encoding nucleic acids. A 60 bp long nucleic acid can only encode a protein of a 20 amino acid long maximum length; such proteins are only about 6% the toal length of the chalcone synthase, "BANYULS" and leucoanthocyanidine reductases of SEQ ID NO:2, 10 and 14, respectively. Thus, 60 bp nucleic acids are too short to encode a chalcone synthase, "BANYULS" or leucoanthocyanidine reductase.

Given the claim breath, unpredictability, and lack of guidance as discussed above, undue experimentation would have been required by one skilled in the art to develop and evaluate the

full scope of claimed nucleic acids, plants transformed with them, and methods of using them to modify CHS, BAN and LAR levels in a plant.

Thus, the instant invention is not enabled throughout the full scope of the claims.

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 65-73 and 75-82 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention. Dependent claims are included in all rejections. The rejection is modified from the rejection set forth in the Office action mailed 22 October 2010, as applied to claims 65-73, 75-77 and 79-82. Applicant's arguments filed 20 December 2010 have been fully considered but they are not persuasive.

Claims 62, 65, 70 and 77 are indefinite in their recitation of "BANYULS (BAN)" as the specification does not define what a BAN protein is.

Applicant urges that BANYULS is used as the full length form of BAN (response pg 12).

This is not found persuasive because the specification does not define what a BAN protein is.

10. Claim 81 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C. 112, 2nd paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

11. No claim is allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anne R. Kubelik, Ph.D., whose telephone number is (571) 272-0801. The examiner can normally be reached Monday through Friday, 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anne Marie Grunberg, can be reached at (571) 272-0975.

The central fax number for official correspondence is (571) 273-8300.

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January 5, 2011

/Anne R Kubelik/
Primary Examiner, Art Unit 1638